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Original research

Infliximab is associated with attenuated immunogenicity to BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD

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ABSTRACT

Objective Delayed second dose SARS-CoV-2 vaccination trades maximal effectiveness for a lower level of immunity across more of the population. We investigated whether patients with inflammatory bowel disease treated with infliximab have attenuated serological responses to a single dose of a SARS-CoV-2 vaccine.

Design Antibody responses and seroconversion rates in infliximab-treated patients (n=865) were compared with a cohort treated with vedolizumab (n=428), a gut-selective anti-integrin α4β7 monoclonal antibody. Our primary outcome was anti-SARS-CoV-2 spike (S) antibody concentrations, measured using the Elecsys anti-SARS-CoV-2 spike (S) antibody assay 3–10 weeks after vaccination, in patients without evidence of prior infection. Secondary outcomes were seroconversion rates (defined by a cut-off of 15 U/mL), and antibody responses following past infection or a second dose of the BNT162b2 vaccine.

Results Geometric mean (SD) anti-SARS-CoV-2 antibody concentrations were lower in patients treated with infliximab than vedolizumab, following BNT162b2 (6.0 U/mL (5.9) vs 28.8 U/mL (5.4) p<0.0001) and ChAdOx1 nCoV-19 (4.7 U/mL (4.9)) vs 13.8 U/mL (5.9) p<0.0001) vaccines. In our multivariable models, antibody concentrations were lower in infliximab-treated compared with vedolizumab-treated patients who received the BNT162b2 (fold change (FC) 0.29 (95% CI 0.21 to 0.40), p<0.0001) and ChAdOx1 nCoV-19 (FC 0.39 (95% CI 0.30 to 0.51), p<0.0001) vaccines. In both models, age ≥60 years, immunomodulator use, Crohn's disease and smoking were associated with lower, while non-white ethnicity was associated with higher, anti-SARS-CoV-2 antibody concentrations. Seroconversion rates after a single dose of either vaccine were higher in patients with prior SARS-CoV-2 infection and after two doses of BNT162b2 vaccine.

Conclusion Infliximab is associated with attenuated immunogenicity to a single dose of the BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines. Vaccination after SARS-CoV-2 infection, or a second dose of vaccine, led to seroconversion in most patients. Delayed second dosing should be avoided in patients treated with infliximab.

Trial registration number ISRCTN45176516.

Significance of this study

What is already known on this subject?

- A growing number of countries, including the UK, have opted to delay second SARS-CoV-2 vaccine doses for all people, trading maximal effectiveness against a lower level of protective immunity across more of the at-risk population. Whether single doses of vaccines are effective in patients treated with antitumour necrosis factor (TNF) therapies is unknown.
- We have previously shown in this cohort that seroprevalence, seroconversion in PCR-confirmed cases and the magnitude of anti-SARS-CoV-2 antibodies following SARS-CoV-2 infection are reduced in infliximab-treated compared with vedolizumab-treated patients.
- Two recent studies have reported that SARS-CoV-2 spike (S) antibody responses are impaired in patients with cancer and transplant recipients treated with chemotherapy and antimetabolite immunosuppressants, respectively. To date, no studies have assessed the effect of anti-TNF therapy on immunogenicity following SARS-CoV-2 vaccination.

INTRODUCTION

Limited SARS-CoV-2 vaccine supplies and pressure on critical care services have forced governments to prioritise primary vaccination to vulnerable groups.

Significance of this study

What are the new findings?

- Anti-SARS-CoV-2 spike (S) antibody concentrations and rates of seroconversion were lower following primary vaccination with both the BNT162b2 and ChAdOx1 nCoV-19 vaccines in patients with inflammatory bowel disease treated with infliximab compared with vedolizumab.
- Older age, immunomodulator use, Crohn's disease (vs ulcerative colitis or inflammatory bowel disease unclassified), and current smoking were associated with lower anti-SARS-CoV-2 antibody concentrations, irrespective of vaccine type. Non-white ethnicity was associated with higher anti-SARS-CoV-2 (S) antibody concentrations following primary vaccination with both vaccines.
- Lowest rates of seroconversion were observed in participants treated with infliximab in combination with an immunomodulator with both the BNT162b2 and ChAdOx1 nCoV-19 vaccines, whereas highest rates of seroconversion were seen in patients treated with vedolizumab monotherapy who received either vaccine.
- Antibody concentrations and seroconversion rates were higher in patients with past SARS-CoV-2 infection prior to a single dose of either vaccine, and after two doses of the BNT162b2 vaccine.

How might it impact on clinical practice in the foreseeable future?

- For patients treated with antitumour necrosis factor (TNF) therapy, particularly for those also treated with an immunomodulator, poor antibody responses to a single dose of vaccine exposes them to a potential increased risk of SARS-CoV-2 infection.
- Higher rates of seroconversion in patients with two exposures to SARS-CoV-2 antigen, even in the presence of TNF blockade, suggest that all patients receiving anti-TNF therapy should be prioritised for optimally timed second doses.
- Until patients receive a second vaccine dose, they should consider that they are not protected from SARS-CoV-2 infection and continue to practice enhanced physical distancing and shielding if appropriate.
- Even after two antigen exposures, a small subset of patients failed to mount an antibody response. Antibody testing and adapted vaccine schedules should be considered to protect these at-risk patients.

In the UK, second vaccine doses have also been delayed, trading maximal effectiveness for a lower level of protective immunity across a greater proportion of the most at-risk population.[1] Consequently, more than half of the adult population have received a single dose of either the RNA vaccine, BNT162b2 (Pfizer/BioNTech) or the adenovirus-vector vaccine, ChAdOx1 nCoV-19 (Oxford/AstraZeneca). Faced with further surges of SARS-CoV-2 infection, a growing number of other countries have also opted to delay second vaccine doses.[2 3]

The inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis (UC) are chronic immune-mediated inflammatory diseases (IMIDs) that affect about 1% of the UK population.[4 5] Treatment typically requires immunosuppression with immunomodulators (azathioprine, mercaptopurine and methotrexate) and/or biological therapies that target disease relevant cytokines or the immune cells that produce them. Antitumour necrosis factor (TNF) drugs, such as infliximab and adalimumab, are the most frequently prescribed biopharmaceuticals used in the treatment of IMIDs. These drugs impair immunogenicity following pneumococcal,[6] influenza[7] and hepatitis B[8] vaccinations and increase the risk of serious infection, most notably with respiratory pathogens.[9] Conversely, vedolizumab, a gut-selective anti-integrin α4β7 monoclonal antibody, is not associated with increased susceptibility to systemic infection or attenuated serological responses to vaccination.[10]

We have recently reported that seroprevalence, seroconversion in PCR-confirmed cases, and the magnitude of anti-SARS-CoV-2 antibodies following SARS-CoV-2 infection are reduced in infliximab-treated compared with vedolizumab-treated patients.[11] We hypothesised that, following at least a single dose with BNT162b2 or ChAdOx1 nCoV-19 vaccine, serological responses would be similarly impaired in patients treated with infliximab compared with vedolizumab arguing against delaying second doses in these patients.

Objectives

We aimed to define, in patients with IBD who had received a COVID-19 vaccination, whether biological class and concomitant use of an immunomodulator impact:

i. Anti-SARS-CoV-2 spike (S) antibody levels.
ii. Rates of seroconversion.
iii. Antibody responses in patients who had previously been infected with SARS-CoV-2 or who had two doses of vaccine.

METHODS

Patient and settings

ImpaCt of bioLogic therApy on saRs-cov-2 Infection and immuniTY (CLARITY) IBD is a UK-wide, multicentre, prospective observational cohort study investigating the impact of infliximab and vedolizumab and/or concomitant immunomodulators (azathioprine, mercaptopurine and methotrexate) on SARS-CoV-2 acquisition, illness and immunity in patients with IBD.

Study methods have been described in detail previously.[11] In brief, consecutive patients were recruited at the time of attendance at infusion units from 92 National Health Service (NHS) hospitals across the UK between 22 September 2020 and 23 December 2020 (online supplemental pp 2–17). The eligibility criteria were age 5 years and over, a diagnosis of IBD, and current treatment with infliximab or vedolizumab for 6 weeks or more, with at least one dose of drug received in the previous 16 weeks. Patients were excluded if they had participated in a SARS-CoV-2 vaccine trial.

Follow-up visits were timed to coincide with biological infusions and occurred approximately 8 weekly. Here, we report vaccine-induced antibody responses at first study visit after primary vaccination, and where possible, after two doses. Participants were eligible for inclusion in our vaccine immunogenicity analysis if they had had a SARS-CoV-2 antibody test within the first 10 weeks after their primary vaccination with any of the available SARS-CoV-2 vaccines.

Outcome measures

Our primary outcome was anti-SARS-CoV-2 anti-spike (S) protein receptor-binding protein antibodies 3–10 weeks after primary vaccination.

Secondary outcomes were:

i. The proportion of participants with seroconversion.

ii. Antibody concentrations and rate of seroconversion in patients with PCR or serological evidence of past SARS-CoV-2 infection.
iii. Antibody concentrations and seroconversion after two doses of vaccine.

Variables

Variables recorded by participants were demographics (age, sex, ethnicity, comorbidities, height and weight, smoking status, and postcode), IBD disease activity (PRO2), SARS-CoV-2 symptoms aligned to the COVID-19 symptoms study (symptoms, previous testing and hospital admissions for COVID-19) and vaccine uptake (type and date of primary vaccination). Study sites completed data relating to IBD history (age at diagnosis, disease duration and phenotype according to the Montreal classifications, previous surgeries and duration of current biological and immunomodulator therapy).[11] We linked our data by NHS number or Community Health Index to Public Health England, Scotland and Wales who archive dates and results of all SARS-CoV-2 PCR tests undertaken. Data were entered electronically into a purpose-designed REDCap database hosted at the Royal Devon and Exeter NHS Foundation Trust.[12] Participants without access to the internet or electronic device completed their questionnaires on paper case record forms that were subsequently entered by local research teams.

Laboratory methods

Laboratory analyses were performed at the Academic Department of Blood Sciences at the Royal Devon and Exeter NHS Foundation Trust. To determine antibody responses specific to vaccination we used the Roche Elecsys Anti-SARS-CoV-2 spike (S) immunoassay[13] alongside the nucleocapsid (N) immunoassay.[14] This double sandwich electrochemiluminescence immunoassay uses a recombinant protein of the receptor binding domain on the spike protein as an antigen for the determination of antibodies against SARS-CoV-2. Sample electrochemiluminescence signals are compared with an internal calibration curve and quantitative values are reported as units (U)/mL.

In-house assay validation experiments demonstrated:

i. The intra-assay and interassay coefficient of variation were 1.3% and 5.6%, respectively.
ii. Anti-SARS-CoV-2 (S) antibodies were stable in uncentrifuged blood and serum at ambient temperature for up to 7 days permitting postal transport.
iii. No effect was observed on recovery of anti-SARS-CoV-2 (S) antibodies following four freeze/thaw cycles.
iv. No analytical interference was observed for the detection of anti-SARS-CoV-2 (S) with infliximab or vedolizumab up to 10 000 mg/L and 60 000 mg/L, respectively, or with antidrug antibodies to infliximab or vedolizumab up to 400 AU/mL and 38 AU/mL, respectively (data not shown).

At entry to CLARITY IBD and at follow-up visits, all patients were tested for previous SARS-CoV-2 infection using the Roche Elecsys anti-SARS-CoV-2 (N) immunoassay. Because antibody responses are impaired following PCR-confirmed natural infection we set a threshold of 0.25 times the Cut-Off Index (COI) at or above which patients were deemed to have had prior infection.[11] We defined a second threshold of 0.12 times the COI, below which patients were deemed to have no evidence of prior infection. Patients with a PCR test confirming SARS-CoV-2 infection at any time prior to vaccination were deemed to have evidence of past infection irrespective of any antibody test result.

Our threshold for seroconversion was defined at Roche Diagnostics (Penzberg, Germany). In brief, anti-SARS-CoV-2 (S) antibodies in 534 serum samples from 210 patients (71 hospitalised with severe COVID-19 and 139 patients with milder disease who were not hospitalised) were correlated with results from the cPass SARS-CoV-2 Neutralisation Antibody Detection Kit (Genscript, Netherlands), a competitive ELISA that reports the proportion of anti-SARS-CoV-2 antibodies that are neutralising.[15] While individuals infected with SARS-CoV-2 develop binding antibodies to the virus, not all develop neutralising antibodies which block cellular infiltration and replication of the virus.[16] In both cohorts, Elecsys Anti-SARS-CoV-2 spike (S) concentrations of greater than or equal to 15 U/mL were associated with neutralisation of ≥20% with a positive predictive value of 99.10% (95% CI 97.74% to 99.64%) (online supplemental figure 1).

Ethical consideration and role of funders

CLARITY IBD is an investigator-led, UK National Institute for Health Research COVID-19 urgent public health study, funded by the Royal Devon and Exeter NHS Foundation Trust, Hull University Teaching Hospital NHS Trust, and by unrestricted educational grants from F. Hoffmann-La Roche AG (Switzerland), Biogen GmbH (Switzerland), Celltrion Healthcare (South Korea), Takeda (UK) and Galapagos NV (Belgium).

None of our funding bodies had any role in study design, data collection or analysis, writing, or decision to submit for publication. Patients were included after providing informed, written consent. The sponsor was the Royal Devon and Exeter NHS Foundation Trust. The protocol is available online at https://www.clarityibd.org. The study was registered with the ISRCTN registry.

Statistics

The sample size for CLARITY IBD was based on the number of participants required to demonstrate a difference in the impact of infliximab and vedolizumab on seroprevalence and seroconversion following SARS-CoV-2 infection, with an estimated background seroprevalence of 0.05. We calculated that a sample of 6970 patients would provide 80% power to detect differences in the seroprevalence of anti-SARS-CoV-2 antibodies in infliximab-treated patients compared with vedolizumab-treated patients, while controlling for immunomodulator status at the 0.05 significance level. We stored and then analysed all serum samples as soon as the Roche Elecsys anti-SARS-CoV-2 (S) immunoassay was established in our laboratory.

Statistical analyses were undertaken in R V.4.0.4 (R Foundation for Statistical Computing, Vienna, Austria). All tests were two tailed and values of $p<0.05$ were considered significant. We included patients with missing clinical data in analyses for which they had data and have specified the denominator for each variable. Anti-S antibody concentrations are reported as geometric means and SD. Other continuous data are reported as median and IQR, and discrete data as numbers and percentages, unless otherwise stated.

Univariable analyses, using t-tests of log-transformed anti-SARS-CoV-2 (S) antibody concentration and Spearman's rank correlation coefficients, were used to identify demographic, disease, vaccine, and treatment-related factors associated with the concentration of anti-SARS-CoV-2 (S) antibodies. To test our primary outcome, we used multivariable linear regression models to identify factors independently associated with log anti-SARS-CoV-2 (S) levels. A priori, we included age, ethnicity,

biological medication and immunomodulator use. No stepwise regression was performed. Results are presented after exponentiation, so that the coefficients of the model correspond to the fold change (FC) associated with each binary covariate. For age, a cut-off was chosen based on graphical inspection of the relationship between age and anti-SARS-CoV-2 (S) antibody concentrations. We also report the proportions of patients who seroconverted following vaccination. Seroconversion was defined as a threshold of 15 U/mL. We conducted sensitivity analyses to compare antibody responses stratified by participants with serological or PCR evidence of SARS-CoV-2 infection at any time prior to vaccination and in those who had received two doses of vaccine.

RESULTS

Patient characteristics

Between September 22 2020 and December 23 2020, 7226 patients were recruited to the CLARITY study from 92 UK hospitals.[11] For the primary immunogenicity analyses we included 865 infliximab-treated and 428 vedolizumab-treated participants without evidence of prior SARS-CoV-2 infection, who had received uninterrupted biological therapy since recruitment and had an antibody test between 21 and 70 days after primary vaccination. Participant characteristics are shown in table 1.

Anti-SARS-CoV-2 (S) antibody level following primary COVID-19 vaccine

Geometric mean (geometric SD) anti-SARS-CoV-2 (S) antibody concentrations were lower in patients treated with infliximab than vedolizumab, following both the BNT162b2 (6.0 U/mL (5.9) vs 28.8 U/mL (5.4) p<0.0001) and ChAdOx1 nCoV-19 (4.7 U/mL (4.9) vs 13.8 U/mL (5.9) p<0.0001) vaccines (figure 1). Among infliximab-treated patients, the geometric mean (geometric SD) anti-SARS-CoV-2 (S) antibody concentrations were also lower in patients treated with a concomitant immunomodulator. Additional univariable analyses are shown in table 2.

In our multivariable models, anti-SARS-CoV-2 antibody concentrations were lower in infliximab-treated patients compared with vedolizumab-treated patients in participants who received the BNT162b2 (FC 0.29 (95% CI 0.21 to 0.40), p<0.0001) and ChAdOx1 nCoV-19 (FC 0.39 (95% CI 0.30 to 0.51), p<0.0001) vaccines. Age ≥60 years, immunomodulator

Table 1 Baseline characteristics of participants who had anti-SARS-CoV-2 spike antibodies measured 3–10 weeks following primary vaccination against SARS-CoV-2

Variable		Infliximab	Vedolizumab	Overall	P value
Vaccine	BNT162b2	44.7% (387/865)	47.2% (202/428)	45.6% (589/1293)	0.41
	ChAdOx1 nCoV-19	55.3% (478/865)	52.8% (226/428)	54.4% (704/1293)	
Age (years)		41.4 (31.5–54.8)	49.6 (37.1–63.8)	43.8 (32.8–57.6)	<0.0001
Sex	Female	50.3% (434/863)	47.1% (200/425)	49.2% (634/1288)	0.19
	Male	49.7% (429/863)	52.7% (224/425)	50.7% (653/1288)	
	Intersex	0.0% (0/863)	0.0% (0/425)	0.0% (0/1288)	
	Prefer not to say	0.0% (0/863)	0.2% (1/425)	0.1% (1/1288)	
Ethnicity	White	91.8% (791/862)	89.9% (381/424)	91.1% (1172/1286)	0.62
	Asian	5.3% (46/862)	7.5% (32/424)	6.1% (78/1286)	
	Mixed	1.9% (16/862)	1.9% (8/424)	1.9% (24/1286)	
	Black	0.7% (6/862)	0.5% (2/424)	0.6% (8/1286)	
	Other	0.3% (3/862)	0.2% (1/424)	0.3% (4/1286)	
Diagnosis	Crohn's disease	65.4% (566/865)	40.7% (174/428)	57.2% (740/1293)	0.00050
	Ulcerative colitis or IBD unclassified	34.6% (299/865)	59.3% (254/428)	42.8% (553/1293)	
Duration of IBD (years)		8.0 (4.0–16.0)	10.0 (5.0–17.8)	9.0 (4.0–16.0)	0.0040
Age at IBD diagnosis (years)		28.8 (21.6–41.8)	34.0 (23.3–47.6)	30.3 (21.9–43.7)	<0.0001
Immunomodulator		61.6% (533/865)	22.0% (94/427)	48.5% (627/1292)	<0.0001
5-ASA		23.0% (199/865)	31.6% (135/427)	25.9% (334/1292)	0.0012
Steroids		3.0% (26/865)	8.4% (36/427)	4.8% (62/1292)	<0.0001
BMI (kg/m^2)		25.9 (22.8–30.6)	26.1 (23.1–30.1)	26.0 (22.9–30.4)	0.75
Heart disease		3.6% (31/865)	6.5% (28/428)	4.6% (59/1293)	0.023
Diabetes		3.8% (33/865)	7.5% (32/428)	5.0% (65/1293)	0.0065
Lung disease		13.5% (117/865)	18.2% (78/428)	15.1% (195/1293)	0.032
Kidney disease		1.2% (10/865)	2.1% (9/428)	1.5% (19/1293)	0.22
Cancer		0.5% (4/865)	2.1% (9/428)	1.0% (13/1293)	0.013
Smoker	Yes	9.7% (84/862)	5.4% (23/425)	8.3% (107/1287)	0.0010
	Not currently	32.0% (276/862)	41.6% (177/425)	35.2% (453/1287)	
	Never	58.2% (502/862)	52.9% (225/425)	56.5% (727/1287)	
Exposure to documented cases of COVID-19		9.4% (81/862)	8.7% (37/425)	9.2% (118/1287)	0.76
Income deprivation score		0.086 (0.052–0.151)	0.084 (0.054–0.141)	0.086 (0.052–0.147)	0.94
Active disease (PRO2)		4.9% (41/831)	11.4% (46/405)	7.0% (87/1236)	<0.0001

Values presented are median (interquartile range) or percentage (numerator/denominator). P values represent the results of a Mann Whitney U, Kruskal Wallis or Fisher's exact test.
5-ASA, 5-aminosalicylic acid; BMI, body mass index; IBD, inflammatory bowel disease; ; PRO2, IBD disease activity.

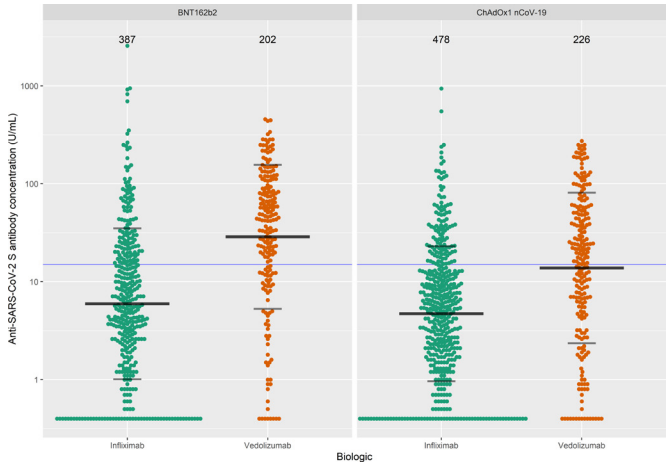

Figure 1 Anti-SARS-CoV-2 spike antibody concentration stratified by biological therapy (infliximab vs vedolizumab) and type of vaccine. The wider bar represents the geometric mean, while the narrower bars are drawn one geometric SD either side of the geometric mean. The threshold shown of 15 U/mL was used to determine seroconversion.

use and current smoking were also independently associated with lower anti-SARS-CoV-2 antibody concentrations in participants who received either vaccine. Conversely, non-white ethnicity was associated with higher antibody concentrations following both vaccines (figure 2).

To allow us to calculate a 15-day rolling geometric mean of anti-SARS-CoV-2 antibody concentrations, we included 2126 participants who had an antibody test carried out between 1 and 63 days after primary vaccination (1427 treated with infliximab and 699 treated with vedolizumab), as shown in figure 3. Three weeks after vaccination, we observed lower anti-SARS-CoV-2 (S) antibody concentrations in infliximab-treated patients compared with vedolizumab-treated patients following both vaccines. Sustained serological responses were observed in the vedolizumab-treated patients but not infliximab-treated patients.

Seroconversion following primary COVID-19 vaccination

The lowest rates of seroconversion were observed in participants treated with infliximab in combination with an immunomodulator with both the BNT162b2 (27.1%; 65/240) or ChAdOx1 nCoV-19 (20.2%; 60/297) vaccines. Highest rates of seroconversion were seen in patients treated with vedolizumab monotherapy who received the BNT162b2 (74.7%;124/166) or ChAdOx1 nCoV-19 (57.3%; 94/164) vaccines (figure 4).

Antibody responses following prior SARS-CoV-2 infection

Among participants with SARS-CoV-2 infection prior to vaccination, geometric mean (SD) anti-SARS-CoV-2 (S) antibody concentrations were lower in infliximab-treated patients compared with vedolizumab-treated patients in those who received a single dose of BNT162b2 (191 U/mL (12.5) vs 1865 U/mL (8.0) p<0.0001) and ChAdOx1 nCoV-19 (185 U/mL (9.3) vs 752 (12.5) p=0.046) vaccines. In both infliximab-treated patients and vedolizumab-treated patients, antibody concentrations following vaccination were higher than those observed in patients without prior infection (figure 5). Overall, across both vaccines, 81.7% (76/93) patients treated with infliximab and 97.1% (33/34) patients treated with vedolizumab seroconverted (p=0.041).

Antibody responses following two COVID-19 vaccine doses

Antibody responses were assessed in 27 patients following two doses of the BNT162b2 vaccine without serological evidence of prior infection (figure 5). In both infliximab- and vedolizumab-treated patients, antibody levels and seroconversion rates were higher after two doses than after a primary vaccine without prior infection (geometric means infliximab 158 U/mL (7.0) vs 6.0 U/mL (5.9), p<0.0001; vedolizumab 562 U/mL (11.5) vs 28.8 U/mL (5.4), p=0.018). After second-vaccine doses, 85% (17/20) infliximab-treated patients and 86% (6/7) vedolizumab-treated patients seroconverted (p=0.68).

DISCUSSION

We have shown that anti-SARS-CoV-2 spike antibody levels and rates of seroconversion are lower following vaccination with a single dose of either BNT162b2 or ChAdOx1 nCoV-19 vaccines in patients with IBD treated with infliximab than vedolizumab. Combination therapy with an immunomodulator further attenuated immunogenicity to both vaccines in infliximab-treated patients. Reassuringly, however, a second exposure to antigen, either by vaccination after infection, or a second dose of vaccine led to seroconversion in most patients.

Direct comparisons between our data and the antibody responses reported in the vaccine registration trials are limited by differences in the assays used to define immunogenicity and the adoption of different thresholds to define seroconversion. No adequately powered studies have reported the effect of anti-TNF drugs on vaccine responses.[17] Our findings are similar, however, to recent reports of the immunogenicity of the BNT162b2 and mRNA-1273 vaccines in transplant recipients and in patients with malignancy treated with antimetabolite immunosuppression, conventional chemotherapy or immune checkpoint inhibitors.[18 19] The authors showed fewer patients treated with potent immunosuppressants seroconverted than healthy controls. Importantly, as we have also shown here, second vaccine doses led to seroconversion in the cancer cohort. However, even after two antigen exposures, a small subset of patients (18% (20/113) infliximab-treated patients and 5% (2/41) vedolizumab-treated patients) in our study failed to mount an antibody response. To identify this group, and because the sustainability of antibody responses overall is unknown, serial measurement of antibody responses is indicated.

Urgent research is needed to understand the factors linked to non-response and how to potentiate long-term immunogenicity in this group. Strategies to be tested include the manipulation of timing of second vaccinations, booster doses, the use of adjuvants and/or switching between vaccines with different mechanisms of action. Moreover, from the public health standpoint, recent case reports have shown that potent immunosuppression leads to chronic nasopharyngeal carriage and evolution of new SARS-CoV-2 variants.[20 21] Whether this occurs in patients treated with anti-TNF therapy with impaired antibody response is an important conceptual concern.

Our data have other important findings relating to SARS-CoV-2 vaccine responses. We have demonstrated that antibody responses to SARS-CoV-2 vaccines are reduced in older individuals and current smokers. Smoking has also been associated with lower antibody responses to hepatitis B vaccination and faster decay of antibodies after vaccination with live attenuated and trivalent influenza vaccines.[22 23] We have also demonstrated higher antibody responses to both the BNT162b2 and ChAdOx1 nCoV-19 vaccines in non-white participants. This might be explained by differences in genetics,[24] gut microbiota,[25]

Table 2 Univariable associations with anti-SARS-CoV-2 spike antibodies, stratified by vaccine type

		BNT162b2		ChAdOx1 nCoV-19	
Variable		**Value**	**P value**	**Value**	**P value**
Biological treatment	Infliximab	6.0 (5.9)	<0.0001	4.7 (4.9)	<0.0001
	Vedolizumab	28.8 (5.4)		13.8 (5.9)	
Immunomodulator in infliximab-treated participants	No	9.7 (4.7)	<0.0001	5.7 (5.1)	0.045
	Yes	4.4 (6.3)		4.2 (4.7)	
Immunomodulator in vedolizumab-treated participants	No	32.4 (5.2)	0.052	15.6 (6.0)	0.082
	Yes	16.7 (6.3)		10.0 (5.5)	
Age (years)		rho=−0.22	<0.0001	rho=−0.15	<0.0001
Sex	Female	9.4 (7.0)	0.092	6.6 (5.5)	0.83
	Male	10.9 (6.3)		6.8 (5.7)	
Ethnicity	White	9.4 (6.6)	0.037	6.2 (5.6)	0.0051
	Asian	20.9 (7.3)		16.1 (5.2)	
	Mixed	25.7 (6.7)		13.7 (5.3)	
	Black	12.5 (1.6)		19.4 (2.2)	
	Other	22.9 (3.7)		5.7 (3.1)	
Diagnosis	Crohn's disease	7.3 (6.4)	<0.0001	5.6 (5.6)	0.0014
	Ulcerative colitis or IBD-unclassified	15.6 (6.5)		8.5 (5.5)	
Duration of IBD (years)		rho=−0.16	<0.0001	rho=−0.12	0.0013
Age at IBD diagnosis (years)		rho=−0.13	0.0021	rho=−0.04	0.25
5-ASA	No	9.8 (6.6)	0.40	6.7 (5.5)	0.93
	Yes	11.5 (7.1)		6.6 (5.9)	
Steroids	No	10.2 (6.7)	0.90	6.8 (5.5)	0.12
	Yes	10.7 (7.3)		4.1 (6.7)	
BMI (kg/m^2)		rho=−0.08	0.068	rho=−0.01	0.81
Heart disease	No	10.3 (6.7)	0.65	6.9 (5.6)	0.010
	Yes	8.7 (7.0)		2.8 (5.2)	
Diabetes	No	10.7 (6.7)	0.0028	6.8 (5.6)	0.066
	Yes	4.1 (4.6)		4.0 (5.2)	
Lung disease	No	10.1 (6.9)	0.70	6.9 (5.5)	0.31
	Yes	10.9 (5.7)		5.7 (6.1)	
Kidney disease	No	10.2 (6.6)	0.60	6.7 (5.5)	0.66
	Yes	15.6 (10.4)		4.7 (12.4)	
Cancer	No	10.4 (6.6)	0.13	6.7 (5.6)	0.069
	Yes	2.0 (9.2)		2.3 (3.6)	
Smoking	Yes	4.7 (7.1)	0.0077	3.4 (4.8)	0.00077
	Not currently	9.4 (6.6)		6.1 (5.4)	
	Never	11.8 (6.5)		8.0 (5.7)	
Exposure to documented cases of COVID-19	No	10.3 (6.7)	0.87	6.6 (5.5)	0.53
	Yes	9.8 (6.8)		7.8 (6.1)	
Income deprivation score		rho=0.01	0.75	rho=0.02	0.65
Active disease (PRO2)	No	10.1 (6.5)	0.32	6.6 (5.4)	0.51
	Yes	14.0 (7.6)		8.1 (7.0)	

Values presented are geometric mean antibody concentration (geometric SD) or Spearman's rho. P values represent the results of an unpaired t-test or test of Spearman's rho.
5-ASA, 5-aminosalicylic acid; BMI, body mass index; IBD, inflammatory bowel disease; VAS, Visual Analogue Scale.

nutrition[26] and priming of the immune system by prior exposure to SARS-CoV-2 not detected by our prevaccination antibody test. Lower antibody concentrations were also observed in patients with Crohn's disease when compared with patients with UC or IBD unclassified. Despite evidence of defective mucosal immunity, previous vaccine studies involving patients with Crohn's disease or UC have not shown attenuated antibody responses to vaccination in the absence of concomitant immunomodulator or biological therapy.[6 7]

The cytokine TNF shapes multiple aspects of host immune responses, including T-cell dependent antibody production. Genetic ablation of TNF results in disruption of B-cell follicles in germinal centres with defective induction of antigen-induced antibody production.[27 28] These biological properties may in part explain why TNF blockade is clinically beneficial in IMIDs, but also explain the increased risk of serious and opportunistic infections and impaired response to other vaccines.

Our findings have important implications for patients treated with anti-TNF drugs particularly those also treated with an immunomodulator. Poor antibody responses to a single dose of vaccine unnecessarily exposes infliximab-treated patients to SARS-CoV-2 infection. However, because we observed higher rates of seroconversion in patients with two exposures to SARS-CoV-2 antigen, even in the presence of TNF blockade,

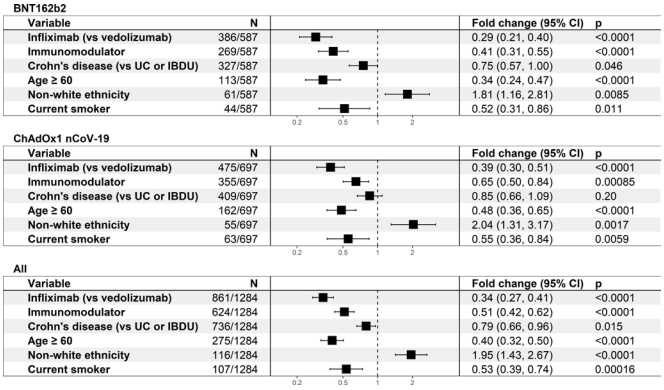

Figure 2 Exponentiated coefficients of linear regression models of log(anti-SARS-CoV-2 spike antibody concentration). The resultant values represent the fold change of antibody concentration associated with each variable. Each vaccine was modelled separately, and then a further model was created using all of the available data. IBDU, inflammatory bowel disease unclassified; UC, ulcerative colitis.

these patients should be prioritised for optimally timed second doses. Until patients receive a second vaccine dose they should consider that they are not protected from SARS-CoV-2 infection and continue to practice enhanced physical distancing and shielding if appropriate.

Limitations

While our data are biologically plausible, we acknowledge the following limitations of our study. We have used an electrochemiluminescence immunoassay to measure antibody concentrations rather than using a neutralising assay. Although neutralisation assays are considered more biologically relevant, it is now established that anti receptor-binding domain antibodies, which target the spike protein component that engages host cells through ligation of ACE 2, closely correlate with neutralisation assays.[29 30] Our validation experiments, comparing anti-SARS-CoV-2 spike (S) concentrations with neutralisation using the cPass test in two cohorts of patients with PCR confirmed SARS-CoV-2 infection,

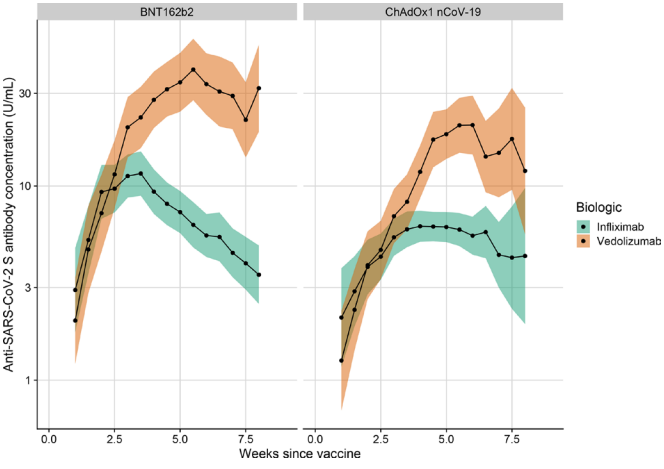

Figure 3 Rolling geometric mean antibody concentration over time, stratified by biological therapy (infliximab vs vedolizumab) and vaccine. Geometric means are calculated using a rolling 15-day window (ie, 7 days either side of the day indicated). The shaded areas represent the 95% CIs of the geometric means. Overall, data from 2126 participants (1427 on infliximab and 699 on vedolizumab) between 1 and 63 days post vaccination are included in this graph .

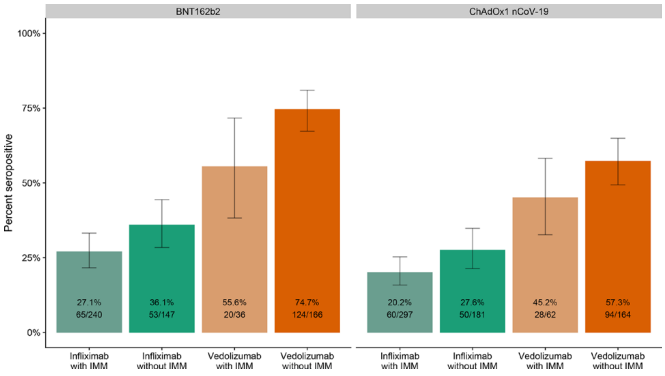

Figure 4 Percentages of participants with seroconversion defined by an anti-SARS-CoV-2 spike antibody concentration ≥15 U/mL, stratified by vaccine, biological and immunomodulator use. Error bars represent the 95% CI of the percentages. IMM, immunomodulator.

confirm this correlation. Second, we only assessed humoral responses to infection, and it is likely that protective immunity additionally requires induction of memory T cell responses. Third, we were unable to investigate whether the timing of biological infusion with respect to vaccination or drug level at the time of vaccination, influences antibody responses. As follow-up blood tests occurred at the time of infusions, which for the vast majority occurred 8 weekly, the time from last infusion to vaccination was negatively correlated with the time from vaccination to the next antibody test, confounding these analyses. Finally, we investigated one anti-TNF drug, infliximab, only. However, we suspect that our key findings will apply to other anti-TNF biologics used to treat IMIDs, including adalimumab, certolizumab, golimumab and etanercept. Further observational data will be required to elucidate the impact of other classes of therapies for IMIDs on SARS-CoV-2 vaccine immunogenicity.

CONCLUSIONS

Infliximab is associated with attenuated immunogenicity to a single dose of the BNT162b2 and ChAdOx1 nCoV-19 SARS-CoV-2 vaccines in patients with IBD. Immunomodulators further blunted immunogenicity rates to both vaccines. Reassuringly, vaccination after infection, or a second dose of vaccine

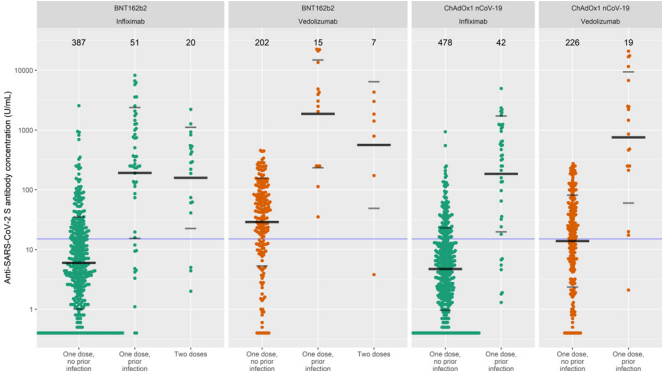

Figure 5 Anti-SARS-CoV-2 spike antibody concentration, stratified by biological therapy (infliximab vs vedolizumab), prior infection and number of doses and type of vaccine. The wider bar represents the geometric mean, while the narrower bars are drawn one geometric SD either side of the geometric mean. The threshold shown of 15 U/mL is the one used to determine seroconversion.

led to seroconversion in most patients. Delayed second dosing should be avoided in patients treated with infliximab.

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Patient and public involvement statement We conducted an electronic survey to gauge the opinion of patients with IBD on the patient questionnaires to be delivered as part of the CLARITY IBD study. We surveyed 250 patients across 74 hospitals. All our proposed questions for study inclusion were rated as important or very important by at least 83% of participants. The Exeter IBD Patient Panel refined the questions included in the study questionnaire, reviewed the study protocol, supported the writing of the patient information sheets, and participated in testing of the electronic consent form and patient questionnaire. A member of the Exeter

IBD Patient Panel sits on the study management committee, ensuring patient involvement in all aspects of study delivery, data analysis and dissemination of findings.

Patient consent for publication Not required.

Ethics approval The Surrey Borders Research Ethics committee approved the study (REC reference: REC 20/HRA/3114) in September 2020.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The study protocol including the statistical analysis plan is available at www.clarityibd.org. Individual participant deidentified data that underlie the results reported in this article will be available immediately after publication for a period of 5 years. The data will be made available to investigators whose proposed use of the data has been approved by an independent review committee. Analyses will be restricted to the aims in the approved proposal. Proposals should be directed to tariq.ahmad1@nhs.net. To gain access data requestors will need to sign a data access agreement.

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